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**Science Global Home Page/Journal Page Title and Rotator Title:** Balancing life and death in cardiomyocytes

**One-Sentence Summary and Rotator Teaser:** Corticosteroid receptor signaling can be beneficial or detrimental to the heart (Oakley *et al.*, in 16 April 2019 issue).

**Overline:** PHYSIOLOGY

**Field Codes:** MEDICINE, PHYSIOLOGY, MOLEC BIOL

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Corticosteroid receptor balance regulates life and death in cardiomyocytes

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### **Abstract**

Mineralocorticoid receptor (MR) antagonists are effective at treating heart failure. In this issue of *Science Signaling*, Oakley *et al.* provide new insight into their cardioprotective actions and highlight the importance of the opposing relationship between the MR and the related glucocorticoid receptor (GR) in the response to cardiomyocyte injury.

Mineralocorticoid receptor antagonists (MRAs) reduce mortality and morbidity in patients with heart failure with reduced ejection fraction, particularly if administered early following myocardial infarction. They are also likely to improve outcomes in some patients with heart failure and preserved ejection fraction (diastolic dysfunction) (1). Cardioprotection in heart failure is independent of any blood pressure effects of MRAs. However, the detailed mechanisms underlying the cardioprotective effects of MRAs and even the cellular locus have been elusive. New research by Oakley *et al.* (2) focused on cardiomyocytes demonstrates the importance of the balance between MR and GR in determining whether damaged cardiomyocytes die or survive.

Aldosterone is generally considered the main ligand for MRs. However, MRAs displace the glucocorticoid cortisol from the heart in humans, not aldosterone (3). Thus, in cardiomyocytes (which lack the glucocorticoid-inactivating enzyme 11 $\beta$ -hydroxysteroid dehydrogenase-2), cortisol - or its mouse equivalent, corticosterone - binds to the higher affinity MR as well as GR. Although both receptors have similar DNA binding specificity, they regulate distinct gene sets and frequently act in opposition (4, 5). The relative roles of MRs and GRs in mediating the cardiac effects of cortisol have been difficult to disentangle. Knock-out of one receptor leaves the other cortisol-signaling pathway intact but unopposed. In a previous study, Oakley *et al.* (6) described mice lacking GR in cardiomyocytes (cardioGRKO) and their premature death from heart failure. This new study asked whether spontaneous disease in cardioGRKO mice resulted from loss of the GR or unopposed MR action. It is probably both. They showed that simultaneous knock-out of the MR (cardioGRMRdKO) alleviated the left ventricular (LV) dysfunction of cardioGRKO and postponed the onset of overt heart failure by several months. This occurred despite similar or worsened inflammation and cardiomyocyte hypertrophy in cardioGRMRdKO mice. Re-expression of MR in cardioGRMRdKO mice partially reversed the cardiac benefits of knocking out the MR (Figure 1).

Key to the findings was the serendipitous choice of the cardiomyocyte-specific  $\alpha$ -myosin heavy chain (MHC) promoter-Cre recombinase transgene to knock-out GR (and MR) in cardiomyocytes. Several groups have reported that MHC-Cre introduces breaks into cellular DNA through Cre recombinase cleavage at cryptic LoxP sites. In the Oakley study, *Dmd* mRNA (which encodes dystrophin) was decreased in hearts of cardioGRKO, cardioMRKO and cardioGRMRdKO mice. This finding is consistent with the age-related loss of dystrophin in hearts of MHC-Cre mice (7) and progressive accumulation of DNA damage in cardiomyocytes due to the MHC-Cre transgene. A strength of the study was the inclusion of MHC-Cre mice as a control in some of the experiments, though not in the measurement of *Dmd* mRNA. A different line of cardiomyocyte GR knock-out mice in which Cre is transiently expressed in cardiomyocytes during development does not develop spontaneous heart failure (8), so the heart failure seen in cardioGRKO mice depends upon the cardiomyocyte injury introduced by Cre recombinase.

DNA damage is proinflammatory and can be catastrophic in cardiomyocytes, which have limited regenerative capacity. Oxidative stress, which is increased in heart failure, also causes DNA damage. Repair of damaged DNA allows cell survival, but if the damage is excessive or cannot be repaired, cell death is triggered. The new study by Oakley *et al.* (2) suggests that the MR and GR are important determinants of the outcome in cardiomyocytes. How? GR-mediated control of cardiomyocyte inflammation is not critical for cardiomyocyte survival, because inflammatory markers were more highly expressed in cardioGRMRdKO hearts. Similarly, markers of cardiomyocyte hypertrophy were as high or higher in cardioGRMRdKO hearts than cardioGRKO hearts. MR deficiency in cardiomyocytes, therefore, does not prevent either inflammation or cardiomyocyte hypertrophy. Does the GR/MR balance impact the decision between cell death and survival? The differential gene analyses certainly support this notion: Expression of genes in cell survival pathways was decreased whereas that of genes in cell death

pathways were increased in cardioGRKO hearts, compared to cardioGRMRKO mice. Moreover, cardioGRKO hearts fared worse than MHC-Cre hearts, consistent with an anti-apoptotic role for GR in cardiomyocytes. Conversely, MR deficiency may protect against apoptosis triggered by DNA damage (or its consequences): LV function was preserved in 6 month old cardioMRKO mice, an age at which MHC-Cre mice show reduced fractional shortening, which is evidence of LV dysfunction and early heart failure (Figure 1). The cell death/survival decisions may be directly regulated by GR and MR or may be indirect and related to differential ion channel remodeling following GR and/or MR activation. Both receptors regulate Ca<sup>2+</sup> currents in cardiomyocytes (as well as in the brain), by distinct mechanisms and in a complex, interdependent, manner. Context is critical in determining the outcomes of cortisol action, such as when the membrane potential is shifted from its resting level (a key issue in excitable cells like cardiomyocytes or neurons), or when tissue damage occurs. In the brain, MR activation by cortisol shapes the early response to stress (akin to a “pro-inflammatory” phase), with GR activation being important for adaptation and recovery (an “anti-inflammatory” phase) (4). Similarly, by acting through both the MR and GR, cortisol controls the spectrum of the cardiomyocyte response to damage. Intriguingly, spironolactone, an MRA in wide clinical use, ameliorates cardiotoxicity during combined chemo- and radiotherapy in a rat model (9) and may attenuate chemotherapy-induced LV dysfunction in breast cancer patients (10), suggesting MRAs may be of clinical benefit in cardiotoxicity induced by radiation or other DNA-damaging agents.

The mice generated by Oakley *et al.* can tell us more. What about females? Cortisol levels and its regulation are sexually dimorphic, which may impact MR/GR activation and outcomes following cardiomyocyte injury. How is diastolic function affected? People with loss-of-function mutations in the MR have better diastolic LV function than normal individuals, despite increased circulating aldosterone levels, suggesting greater preservation of cardiomyocyte number and/or function with decreased MR/GR balance. Answering these questions could help address the wider clinical benefits of MRAs in heart failure.

**Fig. 1. The balance between MR and GR in cardiomyocytes determines the outcome of DNA damage upon heart function.**

Cortisol signalling through MR and GR determines the outcome of DNA damage in cardiomyocytes. Removal of the GR leaves MR signaling unopposed, resulting in progressive loss of cardiomyocytes, left ventricular (LV) dysfunction and heart failure. DNA damage causes oxidative stress, impaired Ca<sup>2+</sup> signaling, decreased cell survival, increased cell death through apoptosis and necrosis. Unopposed GR signaling in the absence of MR preserves LV function in the face of DNA damage. In mice lacking GR, deletion of MR delays the onset of LV dysfunction and heart failure.

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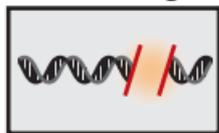
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Cardiomyocyte

DNA damage



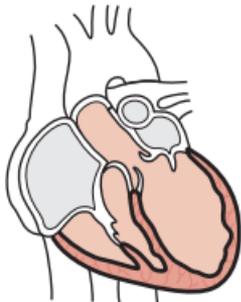
Glucocorticoid receptor



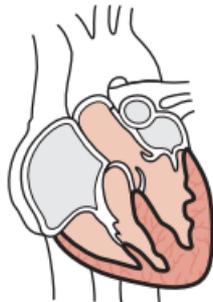
Cortisol



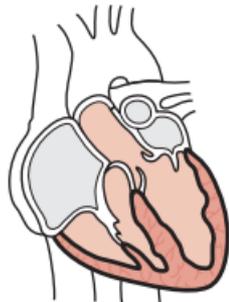
Mineralocorticoid receptor



CardioGRKO



CardioMRKO



CardioGRMRdKO